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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,449	11/17/2003	Ruben Laguens	42597-193226	9366

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VENABLE LLP
P.O. BOX 34385
WASHINGTON, DC 20043-9998

EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
04/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/714,449	**Applicant(s)** LAGUENS ET AL.	
	Examiner Sumesh Kaushal	**Art Unit** 1633	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 05 March 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *5* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *07 April 2008*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☒ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,2,4,10-14,19-27,31,33-44,48-62,64-66,69,71-80 and 98-104*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☒ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Sumesh Kaushal/
Primary Examiner, Art Unit 1633

Continuation of 3. NOTE: Claim 65 recites new claim limitation "VEGF 1-165" which would require additional search/consideration. Newly filed claim 105 would also require additional search/consideration in context to "arteriogenesis" .

Continuation of 11. does NOT place the application in condition for allowance because:

Claims 1-2, 4, 10-14, 19-27, 31, 33-44, 48-62, 64-66, 69, 71-80 and 98-104 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for the reason of record as set forth in the office action (OA) mailed on 10/05/07. Regarding selective targeting of cells in vivo, the applicant argues that the claims (e.g., claim 43) have been amended to clarify that the method of delivery is intramyocardial administration. However the applicant's arguments are found not persuasive because the scope of base claims 1 and 65 is not limited to a method that requires direct intramyocardial administration of the polynucleotide (as claimed). The office action provides clear evidence that gene delivery via any and all routes of administration is considered highly unpredictable (see page 3, OA 10/05/07).
Regarding the treatment of ischemic heart disease, myocardial infarction, myocardial ischemia, dilated cardiomyopathy, heart failure and hypertrophic cardiomyopathy, the applicant argues that the induction of cardiomyogenesis and anteriogenesis clearly indicates that the preceding conditions can be treated by a method of the invention. However as stated in the earlier office action given the scope of invention as claimed the specification as filed fails to disclose the treatment of ischemic heart disease, myocardial infarction, myocardial ischemia, dilated cardiomyopathy, or hypertrophic cardiomyopathy by inducing cardiomyogeneisis via method as claimed. At best the specification teaches the enhaced mitosis if vascular cells and cardiomyocytes (see spec. page 33, lines 27-34). The applicant fails to consider the complexities involved in the etiology of the ischemic heart disease, myocardial infarction, myocardial ischemia, dilated cardiomyopathy, or hypertrophic cardiomyopathy by inducing cardiomyogeneisis. The earlier office action that clearly emphasized that there is need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease especially in context of cardiac gene therapy see OA 01/29/07, page 3, also see Appendix A provided by the applicant). Since the invention as broadly claimed is not considered routine in the art and without sufficient disclosure the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 7311 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 1-2, 4, 10-14, 19-27, 31, 33-44, 48-62, 64-66, 69, 71-80 and 98-104 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Vale et al (Circ. 102:965-974, 2000), for the reason of record as set forth in the office action (OA) mailed on 10/05/07.
The applicant argues that that Vale et al does not teach or suggest that the dose of VEGF-165 which is administered therein is effective to induce cardiomyogenesis and in view of Laham's declaration as a worker of ordinary skill, upon reading the Vale et al. reference, would have recognized that its method would necessarily have stimulated cardiomyogenesis (using low level of plasmid constructs). The applicant argues that the stimulation of cardiomyogenesis is considerably different from merely "improving" the restoration of function to ischemic tissue by augmenting perfusion of the tissue therefore the reference does not suggest or disclose that the dose of VEGFl-165 administered in the reference is effective to induce cardiomyogenesis. However the applicant's arguments are found not persuasive. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e. dosage amount as claimed) is not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).
The applicant furhter argues that the decrease in the size of the ischemic area does not indicate that cardiomyogenesis took place. The applicant argues that Kajstura et al. alleged showing that ischemic myocardium is inherently associated with cardiomyogenesis is incorrect (in view of newly cited references not presented before). However the applicant's arguments are found not persuasive. As stated earlier, Vale et al clearly teaches a gene therapy method that assess efficacy of phVEGF(165) gene transfer in chronic myocardial ischemia. The cited art teaches that the present study constitute additional objective evidence that phVEGF165 GTx augments perfusion of ischemic myocardium, and the results also support the notion that phVEGF165 GTx successfully rescued foci of hibernating myocardium. The applicant fails to consider that cited art provides clear evidence that i) the mean LLS in areas of myocardial ischemia, improved significantly from 9.94±1.53% before phVEGF165 GTx to 15.26±0.98% after phVEGF165 GTx (P=0.004), ii) the area of ischemic myocardium was consequently reduced from 6.45±1.37 cm2 before phVEGF165 GTx to 0.95±0.41 cm2 after GTx (P=0.001), see page 967 col. 2 and Table 2. and iii) that the analysis of LLS in areas of myocardial ischemia, documented marked improvement after GTx. Consequently, the area of ischemic myocardium was reduced to a statistically significant extent. Therefore the cited art provide clear evidence the recovery of cardiac tissue via cardiomyogenesis especially in view of s Kajstura et al who provides clear evidence that ischemic repair involves cardiomyogenesis as there is a "nearly 10-fold increase in this parameter was measured in end-stage ischemic heart disease (152 myocytes per million) and in idiopathic dilated cardiomyopathy (131 myocytes per million), see Kajstura et al, page 8803, fig-2, page 8904 col.1-2). Thus given the broadest reasonable interpretation the cited art clearly anticipates the invention as claimed. .